

INFORMATION DISCLOSURE
STATEMENT BY APPLICANT
Form PTO-1449 (Modified)
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COMPLETE IF KNOWN

Application Number	10/623,189
Confirmation Number	
Filing Date	July 18, 2003
First Named Inventor	DePaoli, Alex M. et al.
Group Art Unit	
Examiner Name	

Sheet 1 of 7 Attorney Docket No. 54113.8005.US02

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	U.S. Patent or Application		Name of Patentee or Inventor of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Figures Appear
		NUMBER	Kind Code (if known)			
EOH	A1	5,521,283				
	A2	5,525,705				
	A3	5,532,336				
	A4	5,552,522				
	A5	5,552,523				
	A6	5,552,524				
	A7	5,554,727				
	A8	5,559,208				
	A9	5,563,243				
	A10	5,563,244				
	A11	5,563,245				
	A12	5,567,678				
	A13	5,567,803				
	A14	5,569,743				
	A15	5,569,744				
	A16	5,574,133				
	A17	5,580,954				
	A18	5,594,101				
	A19	5,594,104				
	A20	5,605,886				
	A21	5,614,379				
	A22	5,691,309				
▼	A23	5,719,266				

EXAMINER <i>/Eileen O'Hara/</i>	DATE CONSIDERED 06/28/2006
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		Office	NUMBER	Kind Code (if known)				
X	B1		EP 725078					
X	B2		EP 725079					
X	B3		EP 736599					
X	B4		EP 741187					
X	B5		EP 744408					
X	B6		EP 745610					
X	B7		EP 835879					
X	B8		WO 96/05309					
X	B9		WO 96/22308					
X	B10		WO 96/23513					
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X	B18		WO 96/31526					
X	B19		WO 96/34111					
X	B20		WO 96/34885					
X	B21		WO 96/35787					
X	B22		WO 96/37517					
X	B23		WO 96/40912					
X	B24		WO 97/00886					
X	B25		WO 97/06816					
X	B26		WO 97/16550					
X	B27		WO 97/18833					
EXAMINER <i>/Eileen O'Hara/ /Eileen O'Hara/</i>				DATE CONSIDERED <i>/Eileen O'Hara/</i>				

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Sheet	3	of	7	Attorney Docket No.	54113.8005.US02
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FOREIGN PATENT DOCUMENTS

		Foreign Patent or Application			
EOH	B28	WO 97/20933			
✓	B29	WO 97/38014			
✓	B30	WO 97/46585			
✓	B31	WO 98/08512			
✗	B32	WO 98/28427			
✗	B33	WO 00/20872			

OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS

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EOH	C1	ABATE, N., et al., "Estimation of Adipose Tissue Mass By Magnetic Resonance Imaging: Validation Against Dissection in Human Cadavers," <i>J. Lipid Res.</i> 1994; 35:1490-6.	
✓	C2	AHIMA, R.S., et al., "Role of Leptin in the Neuroendocrine Response to Fasting," <i>Nature</i> 1996; 382:250-2.	
	C3	ARIOGLU, E., et al., "Efficacy and Safety of Troglitazone in the Treatment of Lipodystrophy Syndromes," <i>An Intern Med.</i> 2000; 133:263-74.	
	C4	BERASAIN, C., et al., "Pathological and Virological Findings in Patients With Persistent Hypertransaminasaemia of Unknown Etiology," <i>Gut</i> . 2000;47:429-35.	
	C5	BERG, A.H., et al., "The Adipocyte-Secreted Protein Acrp30 Enhances Hepatic Insulin Action," <i>Nat Med.</i> 2001; 7:947-53.	
	C6	BOLAN, C., et al., "Intensive, Long-Term Plasma Exchange Therapy For Severe Hypertriglyceridemia in Acquired Generalized Lipoatrophy," <i>J. Clin Endocrin And Metab</i> (Submitted).	
	C7	BURANT, C.F., et al., "Troglitazone Action Is Independent of Adipose Tissue," <i>J. Clin Invest.</i> 1997; 100:2900-8.	
✗	C8	CAMPFIELD, L.A., et al., "Recombinant Mouse OB Protein: Evidence For A Peripheral Signal Linking Adiposity and Central Neural Networks," <i>Science</i> 1995; 269:546-9.	

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EOH	C9	CAO, H., et al., "Nuclear Lamin A/C R482q Mutation in Canadian Kindreds With Dunnigan-Type Familial Partial Lipodystrophy," <i>Hum Mol Genet.</i> 2000; 9:109-12.		
	C10	COSIDINE, R.V., et al., "Serum Immunoreactive-Leptin Concentrations in Normal-Weight and Obese Humans," <i>N Engl J Med.</i> 1996; 334:292-5.		
	C11	EBIHARA, K., et al., "Transgenic Overexpression of Leptin Rescues Insulin Resistance and Diabetes in A Mouse Model of Lipoatrophic Diabetes," <i>Diabetes</i> 2001; 50:1440-8.		
	C12	FAROOQI, I.S., et al., "Effects of Recombinant Leptin Therapy in A Child With Congenital Leptin Deficiency," <i>N Engl J Med.</i> 1999; 341:879-84.		
	C13	FESKANICH, D., et al., "Reproducibility and Validity of Food Intake Measurements From A Semiquantitative Food Frequency Questionnaire," <i>J Am Diet Assoc.</i> 1993; 93:790-6.		
	C14	TRUEBIS, J., et al., "Proteolytic Cleavage Product of 30-Kda Adipocyte Complement-Related Protein Increases Fatty Acid Oxidation in Muscle and Causes Weight Loss in Mice," <i>Proc Natl Acad Sci U S A</i> 2001; 98:2005-L0.		
	C15	GARG, A., et al., "Adipose Tissue Distribution Pattern in Patients With Familiar Partial Lipodystrophy (Dunnigan Variety)," <i>J Clin Endocrinol Metab</i> 1999; 84:170-4.		
	C16	GARG, A., et al., "Peculiar Distribution of Adipose Tissue in Patients With Congenital Generalized Lipodystrophy," <i>J Clin Endocrinol Metab</i> 1992; 75:358-61.		
	C17	GARG, A., et al., "Lipodystrophies," <i>Am J Med.</i> 2000; 108:143-52.		
	C18	GAVRILOVA, O., et al., "Surgical Implantation of Adipose Tissue Reverses Diabetes in Lipoatrophic Mice," <i>J Clin Invest</i> 2000; 105: 271-8.		
↓	C19	GOTTO, A.M., Jr., "Triglyceride As A Risk Factor For Coronary Artery Disease," <i>Am J Cardiol</i> 1998; 82: 22Q25Q.		

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OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS				
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EOH	C20	HALAAS, J.L., et al., "Weight-Reducing Effects of the Plasma Protein Encoded By the Obese Gene," <i>Science</i> 1995; 269:543-6.		T
	C21	HARRISION, L.C., et al., "Correlation Between Insulin Receptor Binding in Isolated Fat Cells and Insulin Sensitivity in Obese Human Subjects," <i>J Clin Invest</i> 1976; 58:1435-41.		
	C22	HEYMSFIELD, S.B., et al., "Recombinant Leptin For Weight Loss in Obese and Lean Adults: A Randomized, Controlled, Dose-Escalation Trial [See Comments]," <i>Jama</i> 1999; 282:1568-75.		
	C23	"Intensive Blood-Glucose Control With Sulphonylureas Or Insulin Compared With Conventional Treatment and Risk of Complications in Patients With Type 2 Diabetes (UKPDS 33)," <i>UK Prospective Diabetes Study (UKPDS) Group, Lancet</i> 1998; 352:837-53.		
	C24	KREISBERG, R.A., "Diabetic Dyslipidemia," <i>Am J Cardiol</i> 1998; 82:67U-73U		
	C25	LAMBRINOUDAKI, I., et al., "Body Composition Assessment By Dual-Energy X-Ray Absorptionmetry: Comparison of Prone and Supine Measurements," <i>Metabolism</i> 1998; 47:1379-82.		
	C26	LAWRENCE, R.D., "Lipodystrophy and Hepatomegaly With Diabetes, Lipaemia, and Other Metabolic Disturbances: A Case Throwing New Light On the Action of Insulin," <i>Lancet</i> 1946; 1:724-731 and 773-775.		
	C27	LUYCKX, F.H., et al., "Non-Alcoholic Steatohepatitis: Association With Obesity and Insulin Resistance, and Influence of Weight Loss," <i>Diabetes Metab</i> 2000; 26:98-106.		
	C28	MAGRE, J., et al., "Identification of the Gene Altered in Berardinelli-Seip Congenital Lipodystrophy On Chromosome 11q13," <i>Nat Genet</i> 2001; 28:365-70.		
↓	C29	MANTON, N.D., et al., "Non-Alcoholic Steatohepatitis in Children and Adolescents," <i>Med J Aust</i> 2000; 173:476-9.		

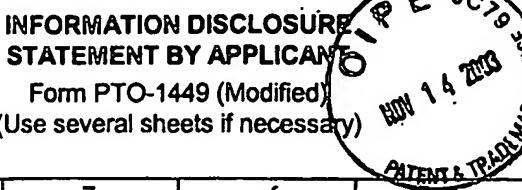
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EOH	C30	MANTZOROS, C.S., et al., "Editorial: Leptin As A Therapeutic Agent-Trials and Tribulations," <i>J Clin Endocrinol Metab</i> 2000; 85:4000-2.		T
	C31	MOITRA, J., et al., "Life Without White Fat: A Transgenic Mouse," <i>Genes Dev</i> 1998; 12: 3168-81.		
	C32	MONTAGUE, C.T., et al., "Congenital Leptin Deficiency Is Associated With Severe Early Onset Obesity in Humans," <i>Nature</i> 1997; 387:903-8.		
	C33	PELLEYMOUNTER, M.A., et al., "Effects of the Obese Gene Product On Body Weight Regulation in ob/ob Mice," <i>Science</i> 1995; 269:540-3.		
	C34	PETERS, A.L., et al., "The New Diagnostic Criteria For Diabetes: The Impact on Management of Diabetes and Macrovascular Risk Factors," <i>Am J Med</i> 1998; 105:15s-19s.		
	C35	REITMAN, M.L., et al., "Lipoatrophy Revisited," <i>Trends Endocrinol Metab.</i> 2000; 11:410-6.		
	C36	SHIMOMURA, I., et al., "Decreased IRS-2 and Increased SREBP-1c Lead To Mixed Insulin Resistance and Sensitivity in Livers of Lipodystrophic and ob/ob Mice," <i>Mol Cel</i> 2000; 6:77-86.		
	C37	SHIMOMURA, I., et al., "Insulin Resistance and Diabetes Mellitus in Transgenic Mice Expressing Nuclear SREBP-1c in Adipose Tissue: Model For Congenital Generalized Lipodystrophy," <i>Genes Dev</i> 1998; 12:3182-94.		
	C38	SHIMOMURA, I., et al., "Leptin Reverses Insulin Resistance and Diabetes Mellitus in Mice With Congenital Lipodystrophy," <i>Nature</i> 1999; 401:73-6.		
	C39	TRYGSTAD, O., et al., "Lipodystrophic Diabetes Treated With Fenfluramine," <i>Int J Obes</i> 1977; 1:287-92.		
▼	C40	UNGER, R.H., et al., "Regulation of Fatty Acid Homeostasis in Cells: Novel Role of Leptin," <i>Proc Natl Acad Sci U S A</i> 1999; 96:2327-32.		

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EOH	C41	UNGER, R.H., et al., "Lipotoxicity in the Pathogenesis of Obesity-Dependent NIDDM, Genetic and Clinical Implications," <i>Diabetes</i> 1995; 44:863-70.		
	C42	YAMAUCHI, T., et al., "The Fat-Derived Hormone Adiponectin Reverses Insulin Resistance Associated with Both Lipoatrophy and Obesity," <i>Nat Med.</i> 2001; 7:941-6.		
	C43	ZHANG, Y., et al., "Positional Cloning of the Mouse Obese Gene and Its Human Homologue," <i>Nature</i> 1994; 372:425-32.		
▼	C44	ZHANG, Y., et al., Correction at Nature , 374:479 (1995).		

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**SUPPLEMENTAL
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EOH	A24	6,258,932		Vahline, et al.		

FOREIGN PATENT DOCUMENTS

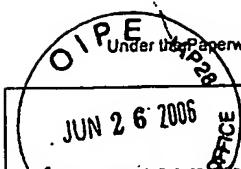
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EOH	C45	BERG, Jens P., "Leptin is a potent Anti-diabetic in Mice with Lipodystrophy and Insulin Resistance," <i>European Journal of Endocrinology</i> 2000; 142:114-116.	
EOH	C46	HADIGAN, Colleen, et al., "Metformin in the Treatment of HIV Lipodystrophy Syndrome," <i>Journal of the American Medical Association</i> July 26, 2000; 284:4:472-477.	

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 (Not for submission under 37 CFR 1.99)

JUN 26 2006	Application Number	10623189
	Filing Date	2003-07-18
	First Named Inventor	Alex M. DEPAOLI
	Art Unit	1646
	Examiner Name	Eileen O'Hara
	Attorney Docket Number	54113.8005.US02

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
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NON-PATENT LITERATURE DOCUMENTS

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Examiner Name	Eileen O'Hara
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JUN 26 2005
140-28
U.S. PATENT & TRADEMARK OFFICE

EOH	1	BERG, J.P., "Leptin is a potent anti-diabetic in mice with lipodystrophy and insulin resistance," European Journal of Endocrinology, Scandinavian University Press, Vol. 142, 2000, pp. 114-116.	<input type="checkbox"/>
EOH	2	EUROPEAN PATENT OFFICE, Supplementary European Search Report for EP 02793811, 2006/03/20.	<input type="checkbox"/>
EOH	3	JAQUET, D. et al., "Extremely low values of serum leptin in children with congenital generalized lipatrophy," European Journal of Endocrinology, Vol. 140, no. 1, Jan. 1999, pp. 107-109.	<input type="checkbox"/>
EOH	4	OGAWA, Yoshihiro et al., "Increased glucose metabolism and insulin sensitivity in transgenic skinny mice overexpressing leptin," Diabetes, Vol. 48, no. 9, Sep. 1999, pp. 1822-1829.	<input type="checkbox"/>
EOH	5	VAN DER MERWE, M. T. et al, "Free fatty acids and insulin levels: Relationship to leptin levels and body composition in various patient groups from South Africa," International Journal of Obesity, vol. 23, no. 9, Sep 1999, pp. 909-917.	<input type="checkbox"/>

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Examiner Signature	/Eileen O'Hara/	Date Considered	07/03/2006
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⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.